PATENT SPECIFICATION

1,093,121

NO DRAWINGS

1,093,121

Date of filing Complete Specification (under Section 3 (3) of the Patents Act 1949) May 21, 1964.

Application Date: May 31, 1963. No. 22027/63.

Application Date: Oct. 1, 1963. No. 38697/63.

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Index at acceptance:—C2 C(2B3A2, 2B3A3, 2B3B, 2B3G3, 2B3G8, 2B30, 2B48C1, 2B48G3 A5 B(2R1, 2S)

Int. Cl.:—C 07 c 103/38

COMPLETE SPECIFICATION

Etherified *p*-Hydroxyanilines

ERRATA

SPECIFICATION No. 1,093,121

Page 1, line 41, *for* "does" *read* "doses"

Page 10, line 32, *for* "formation" *read* "formulation"

THE PATENT OFFICE
4th January 1968

The metabolism of phenacetin is apparently controlled by microsomal enzymes which act primarily by hydroxylation. Thus phenacetin

p-(CH_3.CO.NH).C_6H_4.O.CH_2.CH_3

would first be hydroxylated to give the hemiacetal

p-(CH_3.CO.NH).C_6H_4.O.CHOH.CH_3

which would readily cleave to give paracetamol,

p-(CH_3.CO.NH).C_6H_4.OH

a process which depends on the presence of at least one hydrogen atom on the carbon atom attached to the ether oxygen atom.

Consequently, such a metabolic cleavage could not occur with a tertiary alkyl ether such as *p* - t - butoxyacetanilide or its higher homologues.

p - t - Butoxyacetanilide has been described in the chemical literature but only as a derivative prepared to characterise *p* - t - butoxyaniline, and no biological properties have ever been ascribed to this compound.

It has now been found that *p* - t - butoxyacetanilide has analgesic activity with an absolute potency similar to that of phenacetin but with about four times longer duration of action (24 hours as against 6 hours, judged by the concentration in the blood). There is virtually no detectable formation of paracetamol after its administration, and it is much less toxic than either phenacetin or paracetamol, in that comparably large does cause much less methaemoglobinaemia. Unlike phenacetin, which after chronic administration is metabolised at an increased rate, it appears not to stimulate the production of enzymes for its own destruction. The dose required for this purpose in

[*Price 4s. 6d.*]

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Int. Cl.:—C 07 c 103/38

COMPLETE SPECIFICATION

Etherified *p*-Hydroxyanilines

We, THE WELLCOME FOUNDATION LIMITED of 183—193 Euston Road, London, N.W.1, a company incorporated in England, do hereby declare the invention which was communicated from Burroughs Wellcome & Co. (U.S.A.) Inc., a company incorporated in the State of New York, of 1, Scarsdale Road, Tuckahoe 7, New York, United States of America, for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to etherified *p* - hydroxyanilines which have biological properties.

The common analgesic drug *p* - ethoxyacetanilide (known as phenacetin or acetophenetidine) is rapidly converted *in vivo* into *p* - hydroxyacetanilide (known as paracetamol or A.P.A.P.), which itself is active as an analgesic. It has been generally believed, therefore, that the analgesic action of phenacetin is due to the formation of paracetamol in the body. [See, for example, *The Extra Pharmacopeia* (*Martindale*) Volume I, 24th Edition (1958), at page 25.]

Contrary to this belief, it has now been discovered in experimental animals that phenacetin is an analgesic in its own right and is more powerful than paracetamol. Hence it appears that the metabolic conversion of phenacetin into paracetamol is not only not essential for analgesic activity but may be undesirable, because a weaker analgesic action results; moreover metabolic products are at least partly responsible for the toxic effects seen with phenacetin in overdose or chronic misuse.

The metabolism of phenacetin is apparently controlled by microsomal enzymes which act primarily by hydroxylation. Thus phenacetin

p-(CH_3.CO.NH).C_6H_4.O.CH_2.CH_3

would first be hydroxylated to give the hemiacetal

p-(CH_3.CO.NH).C_6H_4.O.CHOH.CH_3

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Consequently, such a metabolic cleavage could not occur with a tertiary alkyl ether such as *p* - t - butoxyacetanilide or its higher homologues.

p - t - Butoxyacetanilide has been described in the chemical literature but only as a derivative prepared to characterise *p* - t - butoxyaniline, and no biological properties have ever been ascribed to this compound.

It has now been found that *p* - t - butoxyacetanilide has analgesic activity with an absolute potency similar to that of phenacetin but with about four times longer duration of action (24 hours as against 6 hours, judged by the concentration in the blood). There is virtually no detectable formation of paracetamol after its administration, and it is much less toxic than either phenacetin or paracetamol, in that comparably large does cause much less methaemoglobinaemia. Unlike phenacetin, which after chronic administration is metabolised at an increased rate, it appears not to stimulate the production of enzymes for its own destruction. The dose required for this purpose in

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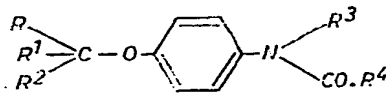
general resembles that of phenacetin, for example about 0.3—1.0 g. in man, although allowance must be made for the more prolonged action as well as for body weight and any individual differences in sensitivity to the drug.

p - t - Butoxyacetanilide has also been discovered to possess another pharmacological property, not shared by phenacetin. Although like phenacetin it acts as an analgesic and to some extent as a soporific at doses of for example 200 mg./kg. in rats and 100 mg./kg. in dogs, at lower doses it appears to be a mild stimulant. For example, at 25 mg./kg. in rats, it reverses the depressant actions of reserpine. It was originally thought that this action might be due to inhibition of the metabolic destruction of catecholamines. However investigations have shown that *p* - t - butoxyacetanilide is not an inhibitor of mono - amine - oxidase (MAO) and so the antidepressant action must have some other cause. The fact that *p* - t - butoxyacetanilide is not a mono-amine-oxidase inhibitor has a considerable advantage since inhibition of that enzyme involves some hazards. Phenacetin may be inactive as an anti-depressant because of its rapid metabolic degradation before much of it can enter the central nervous system.

Analogues of formula (I), as hereinafter defined, also have these properties, and are believed not to be degraded metabolically to the *p* - hydroxy derivative.

Thus the present invention provides a compound of formula (I), other than *p* - t-butoxyacetanilide



(I)

wherein —CRR^1R^2 is a tertiary aliphatic radical containing 4 to 10 carbon atoms in which R, R^1 and R^2 are the same or different and each is a saturated or unsaturated aliphatic hydrocarbon group which may optionally be substituted with one or more hydroxy groups or R and R^1 together may be a cyclic aliphatic hydrocarbon group when R^2 is an aliphatic group as defined above, and R^3 and R^4 are the same or different and each is a hydrogen atom or a lower alkyl group of 1 to 5 carbon atoms. Thus —CRR^1R^2 may for example be t-butyl, 2-methyl-but-2-yl, 3-methylpent-3-yl, 3-ethylpent-3-yl, 2,4,4-trimethylpent-2-yl, 1-methylcyclohexyl, 2-methylbut-3-yn-2-yl, 1-ethynylcyclopentyl, 5-hydroxy-2,5-dimethyl-hex-2-yl, or tetrahydrolinalyl (i.e. 8-hydroxy-2,6-dimethyloct-2-yl).

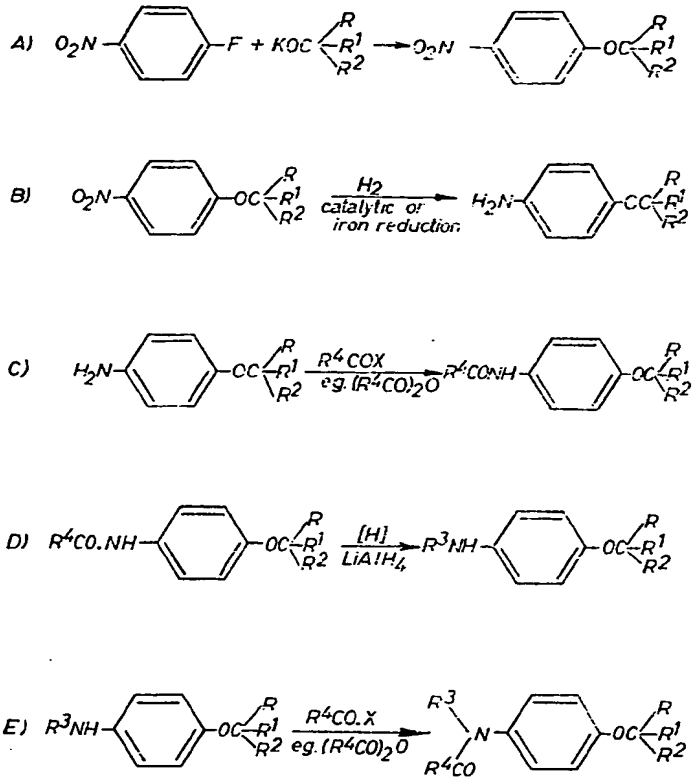
The compounds of formula (I), because they have the tertiary aliphatic group —CRR^1R^2, are not appreciably degraded to paracetamol *in vivo* and they manifest prolonged analgesic activity, as well as antipyretic and anti-depressant activities. It will be appreciated that by using larger aliphatic groups at —CRR^1R^2 and by introducing hydroxy groups into this the fat/water solubility ratio of the compounds can be altered thereby altering the distribution in the body tissue, and this in turn can modify the pharmacological effects. Those variants of formula (I) in which R^3 is a lower alkyl group have certain advantages since they are not readily metabolised to N—OH derivatives. Thus, for example, *p* - t - butoxy - *N* - methylacetanilide [$R=R^1=R^2=R^3=R^4$=methyl] has analgesic potency similar to phenacetin and *p* - t - butoxy - acetanilide but causes no methaemaglobin and is even superior to *p* - t - butoxyacetanilide in this respect. Its anti-depressant activity is less than that of *p* - t - butoxyacetanilide.

The preferred compounds for producing analgesic activity are those wherein R^4 is a methyl group, that is the *N* - acetyl derivatives, for example *p* - (t - butoxy) - *N*-methylacetanilide and *p* - (2 - methylbut - 2 - yloxy)acetanilide. The preferred compounds for producing an anti-depressant or stimulatory effect are those wherein R^4 is hydrogen and $CO.R^4$ is acetyl, for example *p* - (2 - methylbut - 2 - yloxy)acetanilide and *p* - (5 - hydroxy - 2,5 - dimethyl - hex - 2 - yloxy)acetanilide.

An additional activity of some of the compounds of formula (I) and *p* - t - butoxyacetanilide is their ability to kill larval and adult forms of certain liver flukes principally of veterinary importance. For the study of this property the primary screen is against *Fasciola gigantica* in mice. The larval forms of this parasite do not develop into mature worms in rodent hosts but do infest and injure the liver. Compounds showing activity can then be tested in sheep which (with cattle) are the normal and economically important hosts of such parasites. (Liver flukes of man are also of importance in various tropical and oriental regions). The compounds having most marked activity in this respect are *p* - t - butoxyacetanilide, 2 - [*p* - acetamidophenoxy] - 2,5 - dimethyl - 5 - hexanol and 3 - [*p* - acetamidophenoxy] - 2 - methyl - but - 1 - yne.

Other compounds preferred for this type of activity are those of formula (I) in which at least one of R, R^1 and R^2 is an unsaturated aliphatic group. This invention therefore further provides a method for the treatment of a trematode infection in a domestic animal comprising the administration to the host of the infection a therapeutic amount of a compound of formula (I), or *p* - t - butoxyacetanilide.

The compounds of the present invention are prepared by the following route:



Steps D) and E) are relevant only to the preparation of *N* - alkyl derivatives.

Normally step A) is carried out at elevated temperatures, for example 80—150°C, using an excess of the tertiary alcohol $HOCRR^1R^2$ as solvent or sometimes employing 2—3 equivalents of $HOCRR^1R^2$ in toluene; sodium and lithium alcoholates are generally less satisfactory than potassium alcoholates (also referred to as alkoxides). The *p*-fluoronitrobenzene appears to be essential in step A): *p* - chloronitrobenzene gives intractable tars. In steps C) and E) the acylating agent R^4COX is conveniently the anhydride but X may be any suitable proton accepting radical or atom such as halogen, acyloxy, or imidazol - 1 - yl, which are well known to the art. A compound having R^3 as alkyl may also be made by *N* - alkylation of the corresponding compound in which R^3 is hydrogen.

p - t - Butoxyacetanilide or a compound of formula (I) (hereinafter referred to as the "active ingredient") may be presented for administration as pharmaceutical formulations comprising the active ingredient in association with an acceptable carrier therefor. Preferably the formulations are discrete units suitable for oral administration each containing the drug in a predetermined amount, or liquid formulations containing the active ingredient at a predetermined concentration. The term "pharmaceutical formulation" as used herein does not embrace *p* - t - butoxyacetanilide in the form produced in chemical synthesis, or non-sterile solutions or suspensions of the compound in liquids used therein.

A formulation may contain an active ingredient as the sole pharmacologically active substance, or may contain others as well. For example an analgesic preparation may contain acetylsalicylic acid (aspirin) and caffeine together with an active ingredient. One or more carriers may be present in the form well known in the art of pharmacy. For example, solvents, buffers, diluents, flavouring agents, surface active agents, binders, tab-

letting lubricants, antimicrobial agents, antioxidants and other preservatives, colouring matter, or dispersing agents may be included. The formulation may be presented as a tablet, granules, powder, suspension, capsule, or any other form known in the art for presenting analgesics, anti-depressants and trematodicides. A particularly preferred form is a tablet; another preferred form is a dispersable powder or suspension thereof.

These formulations may be made by any of the usual methods employed in pharmacy. In general, they may be made by mixing the active ingredient with one or more carriers and presenting the formulation, preferably as a discrete unit. Thus for example free flowing granules containing an active ingredient may be compressed into tablets.

The following examples illustrate the invention and the preparation of *p* - t - butoxyacetanilide, but are in no way intended to limit the scope of the invention. Where temperatures and pressures are not explicity defined they are to be understood as being in degrees Celsius and millimetres of mercury.

EXAMPLE 1

p-t-Butoxyacetanilide

To a solution of 200 g. (1.8 mole) of potassium t - butoxide in 1200 ml. of t-butanol was added (with external cooling) 254 g. of *p* - fluoro - nitrobenzene. When addition was complete, the solution was stirred and heated on the steam-bath for 15 minutes. The bulk of the t-butanol was distilled off and the oily residue was taken up in benzene, filtered from inorganic salts, and distilled *in vacuo*. The product, *p* - (t-butoxy)nitrobenzene, boiled at 112—114° at 0.4 mm. pressure.

39 g. of the above ether were dissolved in 200 ml. of 95% ethanol containing 12 g. of glacial acetic acid. The solution was hydrogenated using platinum catalyst, and filtered from the catalyst into a flask containing 25 g. of acetic anhydride. The flask was stoppered and allowed to stand with occasional shaking for one hour. The solution was then evaporated *in vacuo* and the residue was washed with petroleum ether. The solid so obtained, *p* - t - butoxyacetanilide, melted at 127—129°. After recrystallization from aqueous alcohol it melted at 131—132°.

EXAMPLE 2

p-t-Butoxyformanilide

A solution of 1,1′ - carbonyldiimidazole (44 g.; 0.21 mole if pure) in dry tetrahydrofuran (300 ml.) was treated dropwise with 98—100% formic acid (12 g.; 0.26 mole) (carbon dioxide was evolved) and stirred for 1 hour at 35°C to give a solution of 1 - formylimidazole. To this was added a solution of dry *p* - t - butoxyaniline (23.5 g.; 0.14 mole) in dry tetrahydrofuran (60 ml.) and dry ether (60 ml.), and the resulting reaction mixture was stirred for 2.5 hours at 30°C After testing to ensure that peroxides were essentially absent, the solvents were evaporated off on the steam bath at reduced pressure (water pump). The residual oil was dissolved in ether and extracted successively with 0.5*N* aqueous hydrochloric acid, water, and aqueous sodium carbonate. The ethereal solution was dried over magnesium sulphate. On evaporation of the solvent, *p* - t - butoxyformanilide (29.5 g.) remained as an oil and proved hard to crystallise. It was eventually crystallised and recrystallised from ether/pentane and appeared to absorb water from the air; after prolonged drying at 61°C at 0.01 mm. it had m.p. 74°C. [Found: C, 68.2; H, 8.0%. $C_{11}H_{15}NO_2$ requires C, 68.4; H, 7.8%.]

EXAMPLE 3

p-t-Butoxypropionanilide

Propionic anhydride (26 g., 0.2 mole) was added dropwise with stirring during approximately 2 minutes to a solution of *p* - t - butoxyaniline (23 g.; 0.14 mole) in anhydrous ether (about 400 ml.). The reaction spontaneously heated the solution to boiling. It was allowed to remain at room temperature overnight and was then distilled on the steam bath at reduced pressure, using first a water pump and then a mechanical pump giving about 1 mm. pressure. The residual clear oil crystallised on cooling, and was recrystallised from ether/hexane to give *p* - t - butoxypropionanilide (26.5 g.) as needles, m.p. 94—96°C. Recrystallisation and prolonged drying at 41°C at 0.01 mm. gave a product of m.p. 101°C. [Found: C, 70.6; H, 8.7%. $C_{13}H_{19}NO_2$ requires C, 70.6; H, 8.7%.]

EXAMPLE 4

p-t-Butoxybutyranilide

A solution of *p* - t - butoxyaniline (22.5 g.) in anhydrous ether (200 ml.) and pyridine (55 ml.) was stirred and treated with butyryl chloride (21.6 g.), using a reflux condenser and a dropping funnel because the solution boiled vigorously. The solution

was stirred for a further hour and then was extracted successively with 1*N* aqueous hydrochloric acid (500 ml.), water, and 3*N* aqueous sodium hydroxide (200 ml.). The ethereal solution was then diluted with an equal volume of ether and about one-third volume of methanol, and dried over magnesium sulphate. Filtration and evaporation of the filtrate left *p* - t - butoxy - butyranilide (30 g.) as an oil which was crystallised and recrystallised from ethanol/water. It was dried for analysis at 61°C at 0.01 mm. and then had m.p. 126—130°C. [Found: C, 71.2; H, 8.9; N, 5.7% $C_{14}H_{21}NO_2$ requires C, 71—4; H, 9.0; N, 6.0%.]

EXAMPLE 5a

p - t - Butoxy - *N* - methylacetanilide by acetylation of *p* - t - butoxy - *N*-methylaniline

A solution of *p* - t - butoxyformanilide (14 g.; 0.07 mole) in anhydrous ether (about 400 ml.) and benzene (40 ml.) was added dropwise with stirring to lithium aluminium hydride (7 g.; 0.18 mole) in anhydrous ether (about 100 ml.), using a reflux condenser protected from atmospheric moisture by sodium hydroxide tube. The turbid reaction mixture was heated under reflux for 17 hours and was then decomposed by the cautious addition of water (19 g.). The solid was filtered off and washed repeatedly with ether. The ethereal solution was washed once with distilled water and then extracted twice with an excess of 0.5*N* aqueous hydrochloric acid. The combined acidic extracts were made alkaline immediately with sodium hydroxide and extracted with ether twice. The ethereal extracts, containing *p* - t - butoxy - *N* - methylaniline in solution, were dried over magnesium sulphate and evaporated to a volume of about 250 ml.

Acetic anhydride (14 ml., an excess) was added dropwise with stirring to this solution. After 1 hour the solvent and excess acetic anhydride were evaporated from the product, which was caused to crystallise by scratching. It was recrystallised by solution in hot ethanol, dilution with approximately 4 volumes of hot water, filtration through hardened filter paper to remove the turbidity, and cooling to 4°C. Scratching and seeding the solution aided in the deposition of the product, *p* - t - butoxy - *N*-methylacetanilide, as glistening platelets. It could be recrystallised from ethanol/water or pentane and had m.p. 80—81°C. [Found: C, 71.2; H, 8.3%. $C_{13}H_{19}NO_2$ requires C, 70.6%; H, 8.7%.]

EXAMPLE 5b)

p - t - Butoxy - *N* - methylacetanilide by methylation of *p* - t - butoxyacetanilide

Sodium amide was prepared from 5.1 g. (0.221 mole) of sodium, 400 ml. of liquid ammonia, and a trace of ferric nitrate in the usual way. A suspension (some had dissolved) of 41.8 g. (0.2 mole) of *p* - t - butoxyacetanilide in 500 ml. of warm dried toluene was added to the sodamide solution during half an hour, followed by 350 ml. of toluene washes. The 'Dry-Ice' (i.e. Solid CO_2) cooled condenser was replaced by a water-cooled condenser, 350 ml. more of toluene were added cautiously with stirring, and the reactants were stirred for an additional hour, by which time the solids were essentially all in solution. The ammonia was now evaporated off, using an ethanol-water heating bath to hasten the process, and nearly all of the remaining ammonia was removed by heating the toluene under reflux for 1½ hours in a slow stream of pure *dry* nitrogen. The grey-white paste so produced was cooled under nitrogen, treated with a solution of 56 g (0.4 *M*) of methyl iodide in 150 ml. of dry toluene, and heated under reflux overnight with stirring. The mixture was filtered and the filtrate, combined with 500 ml. of benzene wash, was evaporated on a steam bath at water-pump pressure to give 46.5 g. of an oily residue, which soon solidified, to a solid of m.p. 74—77°C. This was treated with charcoal in ethanol-water solution, the solvents were distilled off, and the residue recrystallized from an approximately 1 : 4 benzene-hexane mixture, a further crop of product being obtained by seeding the cooled solution and storing it at – 14°C. Two crops of product totalling 33.7 g. and melting point 76.5—78.3°C were obtained, and an additional 10 g. of less pure product was obtained from the mother liquors.

EXAMPLE 6

p - t - Butoxy - *N* - propylacetanilide

By the procedure described in Example 5a) *p* - t - butoxypropionanilide was similarly reduced to give *p* - t - butoxy - N - propylaniline which was acetylated to give *p* - t - butoxy - *N* - propylacetanilide. The product was recrystallised from pentane. In a short-path still, it had b.p. 133°C at 0.01 mm. [Found: C, 72.1; H, 8.9% $C_{15}H_{23}NO_2$ requires C, 72.2; H, 9.3%.]

EXAMPLE 7

p - (2 - Methylbut - 2 - yloxy)acetanilide

The solution of alkoxide made by the addition under a nitrogen atmosphere of

8.3 g. (0.21 mole) of metallic potassium to 400 ml. of 2 - methylbutan - 2 - ol (previously dried over calcium hydride) was stirred, 80 ml. of dried benzene were added, and the solution was treated with 35.5 g. (0.25 mole) of *p* - fluoronitrobenzene, added dropwise to the alkoxide solution initially near its boiling point. The reaction mixture was heated under reflux for an additional 15 hours, cooled under nitrogen, and decomposed *under nitrogen* by the careful addition of 250 ml. of water. The resulting dark solution was partitioned between 0.5*N* aqueous sodium hydroxide and ether. The ethereal solution was dried over anhydrous magnesium sulphate and then distilled. Solvents and unchanged *p* - fluoronitrobenzene were taken off at the water pump using a pressure of 0.03 mm. Hg and temperature of 92°C. A fraction of 2 - (*p* - nitrophenoxy) - 2 - methylbutane boiling at 93—102°C (at pressure of 0.03mm) was collected and totalled 25.9 g.

This was readily reduced to 2 - (*p* - aminophenoxy) - 2 - methylbutane either by iron in ethanol containing a little hydrochloric acid, or by use of hydrogen and Adams' platinum catalyst in ethanol solution. The amine produced by either method was acetylated in ethanolic ethereal solution by addition of acetic anhydride, and the product was obtained as white platelets after evaporation of the solvent. The product recrystallised from ethanol-water or from hexane, and had m.p. 91—94°C or 113—113.5°C (anhydrous). Analysis calculated for $C_{13}H_{19}NO_2$, molecular weight=221.3: C=70.56%, H=8.65%. Found: C=71.33%, 70.16%, H=8.96%, 8.34%.

Example 8

2 - [*p* - Acetamidophenoxy] - 2,5 - dimethyl - hexan - 5 - ol

A solution of 82 g (0.58 mole) of 2,5 - dimethyl - hexan - 2,5 - diol in 300 ml. of dry benzene was treated with 15.6 g (0.39 mole) of metallic potassium, under an atmosphere of dry nitrogen, with efficient stirring to break up the mass of solid which formed as the potassium dissolved. The solution was heated until nearly all the potassium had dissolved (about 2 hours), and then was treated, dropwise, with 30 g. (0.21 mole) of *p*-fluoronitrobenzene dissolved in 100 ml. of dry benzene. After the reaction medium had been heated for an additional hour under reflux, and allowed to stand for 60 hours, it was decomposed with excess water and partitioned between ether and water. Distillation of the dried ethereal layer *in vacuo* gave a fraction which boiled off at a temperature up to 80°C at 7 mm. Hg pressure and this fraction was discarded together with a little solid sublimate and a few drops of liquid boiling off below 154°C (0.2 mm.). The main fraction distilled at 166—168°C at 0.2 mm. pressure and comprised 41.7 g. of an amber-coloured liquid. Slight decomposition had occurred as shown by extraction of about 5% of *p* - nitrophenol from this by alkali.

The distilled *p* - nitrophenyl ether was reduced to the *p* - amino compound either catalytically (hydrogen and Adams' catalyst in ethanolic solution) or with iron and ethanol containing a little hydrochloric acid. This latter procedure was followed by extraction of the amine from ether into dilute aqueous hydrochloric acid, immediate alkalization of the acidic solution, and extraction of the base into ether. The base produced by either method could be acetylated with acetic anhydride, either in ether or methanol solution, and the acetamide compound recrystallized from ether-hexane or from ethanol water, and had m.p. 88—92°C when equilibrated with moist air, or 106—108° if dried at 60° at 0.01 mm. pressure. Analysis calculated for $C_{14}H_{21}NO_3$, molecular weight=255.35: C=68.78, H=9.02. Found: C=68.20, 68.00, H=9.19, 9.00.

Example 9

p - (3 - Methylpent - 3 - yloxy)acetanilide

To the alkoxide prepared under nitrogen from 24 g. (0.613 mole) of potassium, (1.7 mole) of 3 - methylpentan - 3 - ol, and 500 ml. of dry benzene, was added 103 g. (0.73 mole) of *p*-fluoronitrobenzene and 125 ml. dry benzene. The reaction was then heated under reflux for an hour, and worked up as in Example 7, by distilling and retaining a fraction which boiled at 105—115°C (0.03 mm.). There were 88 g. of this liquid, which was redistilled to purify it, and 81.5 g. boiling at 98—105°C (0.015 mm.) were retained.

Reduction of this with Adams' Catalyst and hydrogen in methanol, followed by filtration, and addition of acetic anhydride, gave the anilide. This was crystallized by addition at about 60°C of approximately an equal volume of water to the ethanol solution, followed by cooling and seeding. The product was recrystallized from benzene-hexane and had a melting point of 102.6—104°C (yield analytically pure 33 g.).

Analysis: Calculated for $C_{14}H_{21}NO_2$, molecular weight=235.33; C=71.45, H=8.99. Found: C=71.48, H=9.39.

EXAMPLE 10

N - Ethyl - *p* - t - butoxy acetanilide

N - Ethyl - *p* - t - butoxy aniline was prepared by reduction of *p* - t - butoxy acetanilide with lithium aluminium hydride for 54 hours in refluxing ether and it was isolated by utilising its solubility in dilute acid. From 25 g. of starting material there were obtained 24 g. of liquid. A 19.3 g (0.11 mole) portion of this was acetylated in 200 ml. of anhydrous ether by addition of 20.4 g. (0.2 mole) of acetic anhydride in 50 ml. of ether. After the spontaneous refluxing had stopped heating of the reactants under reflux was continued for an additional two hours, and then the mixture was distilled on the steam bath, finally at 0.1 mm. pressure. The residue was an oil which was taken up in hexane and cooled in 'Dry-Ice' (Solid CO_2). The crystals which formed were filtered off and recrystallized from pentane, again cooling up to $-78°C$. The product, which was analytically pure material, appeared to melt at 50—53°, and was a single substance on examination by gas-liquid chromatography ("Vapor Phase Chromotography").

Analysis calculated for $C_{14}H_{21}NO_2$, molecular weight = 235.33: C = 71.45, H = 8.99, N = 5.95. Found: C = 72.23, H = 9.42, N = 5.93.

EXAMPLE 11

p - (2 - Methylbut - 3 - yn - 2 - yloxy)acetanilide

A suspension of 34 g. of potassium hydride in 250 ml. of dry toluene was prepared starting from commercial grade 50% suspension of potassium hydride in mineral oil which had been washed free of mineral oil with dry toluene under a nitrogen atmosphere. To this suspension 500 g. of 2 - methyl - but - 3 - yn - 2 - ol were added by dropwise addition. The reaction mixture temperature was maintained at 60°C and stirred during the dropwise addition of 150 g. (1.07 mole) of *p* - fluoronitrobenzene, and for 5 days more. The usual purification, consisting of dilution with water, extraction into ether, extraction of *p* - nitrophenol from the ethereal solution with 0.3 *N* aqueous Sodium hydroxide, and evaporation of the dried ethereal solution, gave a pasty residue from which 26 g. of 2,5 - dimethylhex - 3 - yn - 2,5 - diol as an undesired by-product were separated by filtration and washing with a little hexane. The filtrate was distilled twice and the fraction distilling at 96—100°C (0.01 mm.) was maintained. This was *p* - (2 - methylbut - 3 - yn - 2 - yloxy)nitrobenzene.

Analysis calculated for $C_{11}H_{11}NO_3$, molecular weight = 205.21: C = 64.38, H = 5.40. Found: C = 64.78, H = 4.99.

Reduction of 30 g. of this nitro-compound in 200 ml. of 95% ethanol by 7.8 ml. of concentrated hydrochloric acid and 67.5 g. of iron powder added immediately after the acid gave, after alkalization and steam distillation, 18 g. of a yellow weakly basic oil. This was readily characterized even in its crude form, as it gave 88% of the theoretical acetylene titre by the method of S. Siggia, "Quantitative Organic Analysis via Functional Groups" John Wiley and Sons, N.Y., 1949 Ed., P.55.

Acetylation of this amine by means of excess of acetic anhydride and recrystallization of the resulting acetamino - compound from ether - hexane gave 7 g. of white crystals, m.p. 83—84°C.

EXAMPLE 12

Tablets containing 300 mg. of drug.

Per tablet:—

(a)	*p* - t - butoxyacetanilide sifted at aperture size 124 μ	300 mg
(b)	potato starch	45 mg.
(c)	dioctyl sodium sulphosuccinate	0.35 mg.
(d)	magnesium stearate	3.0 mg.
		348.35 mg.

A starch mucilage containing the (c) was made with part of the (b). The remainder of the (b) was mixed with the (a), and the mixture was granulated with the mucilage. The granules were sifted at aperture size 1130 μ, dried and sifted at aperture size 1130 μ. The dried granules were then mixed with the (d) and compressed on a suitable tabletting die into tablets for use in producing analgesia.

EXAMPLE 13

Tablets containing 100 mg. of drug.

Per tablet:—

(a)	*p* - t - butoxyacetanilide sifted at aperture size 124 μ	100 mg.
(b)	potato starch	15 mg.
(c)	polyoxyethylene sorbitan monolaurate	0.1 mg.
(d)	magnesium stearate	1.0 mg.
		116.1 mg.

A starch mucilage was made containing the (c) with part of the (b). Half the remainder of the (b) was added to the (a) and the mixture was granulated with the mucilage. The granules were sifted at aperture size 1130 μ, dried, and sifted at aperture size 1130 μ. The dried granules were then mixed with the (d) and the remainder of the (b) and compressed on a suitable tabletting die into tablets for use in producing anti-depressant effects.

EXAMPLE 14

Tablets containing 100 mg. of drug.

Per tablet:—

(a)	*p* - t butoxyacetanilide sifted at aperture size 124 μ	100 mg.
(b)	lactose in fine powder	100 mg.
(c)	potato starch	20 mg.
(d)	magnesium stearate	2 mg.
		222 mg.

A mixture containing the (a), the (b), and half the (c) was granulated with a 10% gelatin solution in aqueous alcohol. The granules were sifted at aperture size 965 μ and dried. The (d) and the remainder of the (c) were added, and the mixture was sifted at aperture size 965 μ and compressed on a suitable tabletting die.

EXAMPLE 5

Compound tablets.

Per tablet:—

(a)	*p* - t - butoxyacetanilide sifted at aperture size 124 μ	150 mg.
(b)	anhydrous caffeine	30 mg.
(c)	codeine phosphate	8 mg.
(d)	potato starch	50 mg.
(e)	acetylsalicylic acid in fine free-flowing crystals	250 mg.
(f)	sodium lauryl sulphate	7 mg.
		495 mg.

All the ingredients except the (f) were mixed and granulated by precompression. The granules were sifted at aperture size 1130 μ, mixed with the (f), and compressed on a suitable tabletting die into tablets for use in producing analgesia.

EXAMPLE 16

Compound tablets.

Per tablet:—

(a)	*p* - t - butoxyacetanilide sifted at aperture size 124 μ	150 mg.
(b)	anhydrous caffeine	30 mg.
(c)	potato starch	50 mg.
(d)	acetylsalicylic acid in fine free-flowing crystals	250 mg.
(e)	sodium lauryl sulphate	7 mg.
		487 mg.

The (a), the (b) and half of the (c) were mixed and granulated with a starch mucilage made with part of the (c). The granules were sifted at aperture size 1130 μ, dried, and

sifted at aperture size 1130 μ. The dried granules were then mixed with the (d), the (e) and the remainder of the (c) and compressed on a suitable tabletting die.

EXAMPLE 17
Capsules.

Per capsule:—

(a)	*p* - t - butoxyacetanilide sifted at aperture size 124 μ	75 mg.
(b)	anhydrous caffeine	15 mg.
(c)	codeine phosphate	4 mg.
(d)	acetylsalicylic acid sifted at aperture size 124 μ	125 mg.
		219 mg.

The ingredients were mixed thoroughly and the mixture was filled into hard gelatin capsules which then were sealed.

EXAMPLE 18
Powders

Per powder paper:—

(a)	*p* - t - butoxyacetanilide sifted at aperture size 124 μ	150 mg.
(b)	anhydrous caffeine	30 mg.
(c)	codeine phosphate	8 mg.
(d)	acetylsalicylic acid sifted at aperture size 124 μ	250 mg.
(e)	sodium lauryl sulphate	6 mg.
		444 mg.

The ingredients were mixed thoroughly and the mixture was wrapped in powder papers, to be taken as a draught by stirring into water.

EXAMPLE 19
Syrup

per 100 ml.:—

(a)	*p* - t - butoxyacetanilide in fine powder	5 g.
(b)	sucrose distearate	0.1 g.
(c)	vanillin	0.04 g.
(d)	glycerol	20 g.
(e)	methyl - *p* - hydroxybenzoate	0.1 g.
(f)	n - propyl p - hydroxybenzoate	0.1 g.
(g)	sucrose, 66.7% w/w in water, to 100 ml.	

This flavoured syrup, containing 50 mg. of drug per per ml., is especially suitable for paediatric use.

EXAMPLE 20

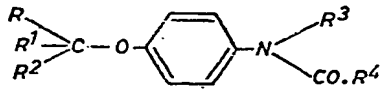
Formulations similar to those described in Examples 12—19 were prepared using *p* - (2 - methylbut - 2 - yloxy)acetanilide.

EXAMPLE 21

Formulations similar to those described in Examples 12 and 15—19 were prepared using *p* - t - butoxy - *N* - methylacetanilide.

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein —CRR^{1}R^2 is a tertiary aliphatic radical containing 4 to 10 carbon atoms in which R, R^1 and R^2 are the same or different and each is a saturated or unsaturated aliphatic hydrocarbon group which may optionally be substituted with one or more hydroxy groups or R and R^1 together may be a cyclic aliphatic hydrocarbon group

when R^2 is an aliphatic group as defined above, and R^3 and R^4 are the same or different and each is a hydrogen atom or a lower alkyl group of 1 to 5 carbon atoms, other than *p* - t - butoxyacetanilide.

2. A compound as claimed in claim 1 wherein R^4 is an alkyl group.

3. A compound as claimed in claim 2 in which R^4 is a methyl group.

4. A compound as claimed in claim 1 in which R^3 is a hydrogen atom and R^4 is a methyl group.

5. A compound as claimed in claim 1 in which $—CRR^1R^2$ is a tertiary - butyl group, R^4 is a methyl group, and R^2 is a lower alkyl group of 1 to 5 carbon atoms.

6. A compound as claimed in claims 1, 2 or 3 wherein at least one of R, R^1 and R^2 is an unsaturated aliphatic group.

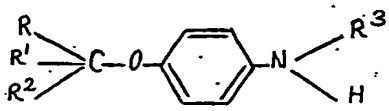
7. *p* - t - Butoxy - *N* - methylacetanilide.

8. 2 - (*p* - Acetamidophenoxy) - 2,5 - dimethyl - hexan - 5 - ol.

9. *p* - (2 - Methylbut - 3 - yn - 2 - yloxy)acetanilide.

10. *p* - (2 - Methylbut - 2 - yloxy)acetanilide.

11. A method for the preparation of a compound claimed in any of claims 1 to 10 comprising the reaction of a compound $R^4CO.X$ with a compound



wherein R, R^1, R^2, R^3 and R^4 have the above defined meanings and X is a proton-accepting atom or radical such as a halogen atom or acyloxy group, and the further optional step of alkylating in known manner the product of this reaction in the case where R^3 is a hydrogen atom to replace this by a lower alkyl group of 1 to 5 carbon atoms.

12. A method as claimed in claim 11 wherein R^4 is an alkyl group.

13. A method as claimed in claim 11 wherein R^4 is a methyl group and R^3 is a hydrogen atom.

14. A method as claimed in claim 11 wherein $R^4CO.X$ is an acid anhydride.

15. A method as claimed in claims 11 and 14 for the preparation of *p* - (2-methylbut - 3 - yn - 2 - yloxy)acetanilide.

16. A pharmaceutical formulation comprising a compound defined in any of claims 1 to 10 in association with an acceptable carrier therefor.

17. A pharmaceutical formation comprising *p* - t - butoxyacetanilide in association with an acceptable carrier therefor.

18. A formulation as claimed in claim 16 or 17 suitable for use in oral administration.

19. A formulation as claimed in claim 18 wherein the formulation is a tablet.

20. A formulation as claimed in claim 18 wherein the formulation is in the form of a powder either suspended in a liquid or ready for suspension in a liquid.

21. A formulation as claimed in claim 16 wherein the carrier is a surface active agent and a solvent.

22. A method for preparing a pharmaceutical formulation as claimed in any of claims 16 to 21 comprising admixture of the active ingredient with the carrier therefor.

23. A method for the treatment of a trematode infection in a domestic animal comprising the administration to the host of the infection a therapeutic amount of a compound defined in any of claims 1 to 10, or *p* - t - butoxyacetanilide.

24. A method as claimed in claim 25 comprising the administration of a compound defined in claim 6.

25. A therapeutically active etherified *p* - hydroxy - *N* - acylaniline claimed in claim 1 substantially as heinbefore described with particular reference to the Examples 2 to 11.

26. A method, substantially as hereinbefore described with particular reference to Examples 2 to 11, for the preparation of a therapeutically active etherified *p*-hydroxy-*N*-acylaniline claimed in claim 1.

27. A pharmaceutical formulation of an etherified *p* - hydroxy - *N* - acylaniline substantially as hereinbefore described with particular reference to Examples 12 to 21.

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